Remarks / Arguments

I.

Introduction to the Invention

The present invention provides a blocking reagent having at least one photoreactive group for covalent immobilization on a sensor surface. Since the blocking reagent itself includes a photoreactive group for immobilization, the blocking reagent may be bound to the sensor surface without an intermediate crosslinking layer. Further, since a crosslinking layer is no longer required traditional masking techniques that selectively expose portions of the crosslinking layer for irradiation are also no longer required.

II.

Response to Claim Rejections Under 35 USC §103

A. Standard for Obviousness

As indicated by the examiner a proper obviousness rejection requires consideration of the factual inquiries provided in Graham v. John Deere Co., 38 U.S. 1, 148 USPQ 459 (1966), including: 1) determining the scope and contents of the prior art; 2) ascertaining the differences between the prior art and the claims at issue; 3) resolving the level of ordinary skill in the pertinent art; and 4) considering objective evidence present in the application indicating obviousness or nonobviousness. Although Graham v. John Deere requires that certain factual inquiries be conducted to support a determination of the issue of obviousness, the actual determination of the issue requires an elevation in light of the findings in those inquiries as to the obviousness *of the claimed invention as a whole*, not merely the differences between the claimed invention and the prior art. Lear Siegelr, Inc. v. Aeroquip Corp., 221 USPQ 1025, 1033 (Fed. Cir. 1984).

B. Claims 79-80 Are Not Obvious Under 35 U.S.C. § 103(a) by Cohen et al. (US 2003/0207258) in view of Pomato et al. (US 5,965,106) further in view of Clapper (US 5,744,515) and light of Kamb et al. (US 2003/0027214)

The examiner rejects claims 79-80 under 35 U.S.C. § 103(a) as being obvious over Cohen et al. in view of Pomato et al. further in view of Clapper and in light of Kamb et al. Specifically, the examiner argues Cohen et al. include a crosslinking reagent immobilized on a substrate and having a photoreactive group for attachment to a blocking reagent. The examiner also cites Cohen et al. as teaching a photoreactive crosslinking agent of SANPAH. The examiner acknowledges Cohen et al. fail to teach the blocking reagent having the photoreactive group for covalent immobilization on a surface and the photoreactive group being benzophenone.

The examiner cites Kamb et al. as teaching a covalent bond formed between a photoreactive SANPAH and substrate when SANPAH is photoactivated and adds that Pomato et al. teach photoreactive benzophenone being advantageous over a photoreactive group of arylazide reagents, such as SANPAH. Further, the examiner adds that Clapper teaches a molecule having a photoreactive group, including benzophenone, for covalent immobilization to a substrate.

Thus, the examiner concludes that it would have been obvious to alter Cohen et al. to include a photoreactive group on the blocking reagent instead of the substrate since Clapper teaches a photoreactive group for covalent immobilization on a surface and would have been obvious to substitute benophenone instead of SANPAH as taught by Kamb et al and Pomato et al. Accordingly, the examiner concludes claims 79 and 80 are obvious.

B1. With respect to all claims, Clapper does not teach covalent immobilization of a blocking reagent on a sensor substrate using a photoreactive group but instead teaches crosslinking of adhesion molecules using a photoreactive group and the physical entrapment of the crosslinked adhesion molecules within pores of a porous substrate

The examiner proposes reconfiguring the system of Cohen et al. to provide a photoreactive group on the blocking reagent for binding to the substrate instead of providing the photoreactive group as part of a crosslinking layer that is applied to the substrate prior to the addition of both the receptive and blocking materials. In support of this reconfiguration, the examiner argues that in Clapper a molecule having a photoreactive group is covalently immobilized to a substrate. However, closer inspection reveals that in Clapper adhesion molecules are crosslinked to one another through the photoreactive group then physically entrapped within the pores of an implant substrate. Clapper is considered in more detail below.

Clapper teaches a porous biomaterial that promotes endothelialization for use as an implant or vascular graft. This is accomplished in part by adding adhesion molecules to a suitable substrate, such as expanded polytetrafluoroethylene (ePTFE). The adhesion molecules promote cell attachment and migration into the pores of the substrate, which ultimately results in the formation of capillaries within the pores. Thus in Clapper, the pores of the biomaterial are themselves targeted by the adhesion molecules. That is, the Clapper system relies in part on a biomaterial that is sufficiently porous. This is discussed in col. 8, l. 67 through col. 9, l. 27, which provides.

> "Given the present specification, those skilled in the art will be able to identify and fabricate devices using biomaterials having a suitable combination of porosity and rigidity.
>
> Biomaterials are preferably suitably porous to allow the attachment and migration of cells, which may be followed by the formation and growth of capillaries into the surface. Suitable pores can exist in the form of small channels or passages which start at an external surface and extend partially or completely through the biomaterial. In such cases, the cross-sectional dimensions of the pores are larger than the diameter of a capillary (5μm) and are typically less than 1 mm. Interconnecting pores are preferable to pits (nonconnecting pores).
>
> Preferably, in turn, the average diameter of such pores ranges from about 5 μm to about 1 mm. The porosity must be sufficiently large to allow capillary endothelialization: therefore the average diameter of individual pores should be greater than about 5 μm. The upper pore size value is not critical so long as the biomaterial retains sufficient rigidity, however, it is unlikely that a useful device would have an average pore size of greater than about 1 mm. Such pore dimensions can be quantified by microscopic examination.

> With a preferred biomaterial such as an ePTFE material the porosity can be determined for the internodal areas of the material. The internodal distance and the node widths are also useful factors, not only in determining the overall porosity, but in determining the strength of the material as well." (emphasis added)

Thus, from Clapper it appears there are specific requirements regarding the substrate material. Mechanistically, closer inspection of Clapper also reveals immobilization of the adhesion molecules occurs by crosslinking the adhesion molecules themselves then physically entrapping them in the pores. Clapper reasons that ePTFE, which is known to be porous, has few abstractable hydrogens. This is summarized at col. 13, ll. 16-31, which provides.

> "As described in greater detail below, three adhesion molecules (fibronectin, laminin, and type IV collagen) were obtained from commercial sources and photoderivatized by covalent attachment of a photoactivatible latent reactive group. The proteins were then added to a porous vascular graft device formed from expanded polytetrafluoroethylene (ePTFE). The proteins were illuminated to activate the photoactivatible latent reactive groups and produce covalent immobilization to the ePTFE device.
>
> ePTFE has a low content of abstractable hydrogens; therefore, the mechanism of photoimmobilizing the adhesion molecules to ePTFE is believed to occur primarily via crosslinking of adjacent adhesion molecules. In turn, the covalently crosslinked network of adhesion molecules is immobilized via physical entrapment within the porosity of the ePTFE." (emphasis added)

Since ePTFE has few abstractable hydrogens, Clapper covalently crosslinks the adhesion molecules and physically entraps them in pores of the porous substrate. Still closer inspection reveals that Clapper actually uses an adsorption step for attachment of the adhesion molecules to the ePTFE itself. For example, referring to col. 14, ll. 9-12,

> "Solutions of photoderivatized proteins were added to ePTFE, allowed to adsorb for 2 hours at room temperature, and illuminated at 320 to 340 nm to activate the BBA moieties and produce covalent coupling." (emphasis added)

Since Clapper provides a photoreactive group for crosslinking the adhesion molecules to one another and adsorption of the adhesion molecules to the ePTFE surface, one skilled in the art would not combine Clapper with Cohen et al. to provide a blocking reagent with a photoreactive group for covalent immobilization on a sensor surface. Accordingly, Applicant respectfully requests the rejection be withdrawn and the claims allowed.

> B2. With respect to all claims, one skilled in the art would not look to the immobilization technique described in Clapper for use with Cohen et al. since central to Clapper is the use of a highly porous substrate with areas of high concentration of adhesion molecules to attract cells into pores; whereas central to Cohen et al. is the uniform covering of molecules across the entire substrate

As discussed above, Clapper uses ePTFE as a grafting substrate or implant. Clapper also describes ePTFE as a highly porous material. As cited above, "In such cases, the cross-sectional dimensions of the pores are larger than the diameter of a capillary (5μm) and are typically less than 1 mm." Again, the object of Clapper is to attract cells into pores. This is accomplished by physical entrapment of adhesion molecules within the pores. Thus, although the examiner suggests the interchangeability between the Cohen et al. and Clapper methods, the differences between the substrates themselves suggest the techniques are in fact substrate dependent. That is, Clapper is particularly designed for use with highly porous substrates to permit entrapment of crosslinked adhesion molecules. The result in Clapper is a high concentration of adhesion molecules localized at the pores. As such, the substrate itself is not uniformly coated but instead varies depending on its three dimensional structure.

In contrast, central to Cohen et al.'s method is to uniformly cover the substrate with either blocking or receptive materials. This is summarized at paragraph [0048],

> "The receptive material and blocking material may be applied to the substrate over the photo-reactive crosslinking agent by any conventional method. The material is applied so that it generally uniformly covers an entire (for example, upper) surface of the substrate." (emphasis added)

Thus, whereas Clapper's immobilization technique itself results in areas of increased concentration of adhesion molecules. Cohen et al. do not desire such an approach. Instead, Cohen et al. seek to uniformly distribute receptor or blocking material across regions of the substrate. As a result, each uses a different technique for immobilization to fulfill the corresponding goals.

Further, although modifications to Cohen et al. may be performed by those skilled in the art, it is likely that such modifications would retain the object of increased sensitivity and thus continue with an approach of covering the substrate uniformly. Since uniform covering would likely be desired it is unlikely one skilled in the art would seek to modify the system using implant technology which attempts to increase localization of adhesion molecules for recruitment of cells into pores.

Since the substrates themselves are vital to the development of appropriate bonding compounds as taught by both Clapper and Cohen et al. and the substrates themselves are significantly different, one skilled the art would not combine the techniques used to entrap compounds within porous substrates with those for uniformly covering a substrate. As such, one skilled in the art would not apply the methods of Clapper to the blocking reagent and substrate of Cohen et al. Accordingly, Applicant respectfully requests the rejection be withdrawn and the claims allowed.

B3. With respect to all claims, a different technical approach is provided in the present application in comparison to Cohen et al., which does not require photo-masking

While the examiner proposes combining elements from both implant technology and diagnostics technology to form the blocking reagent for a sensor as set forth in the claims, viewing the technical approaches as a whole, the present application provides a new approach for the immobilization of a blocking reagent, which itself supports a finding of non-obviousness.

The object of Cohen et al. is to increase the sensitivity of analyte detection; however, the approach remains consistent with traditional photo-masking approaches.

That is, Cohen et al. continue the traditional approach of photo-masking together with irradiation steps to define capture and blocking zones on the sensor. This approach is summarized at paragraph [0031],

> "The present invention comprises, in broad terms, a process of defining an active pattern of analyte-specific receptive material on a substrate surface by photo-masking the substrate."

That is, central to Cohen et al. is the technical approach taken, which is to improve photo-masking techniques themselves. For instance, Cohen et al., proceed to detail steps required in the photo-masking process. For instance paragraphs [0031]-[0032] provide,

> "A layer containing a photo-reactive crosslinking agent is first applied to a surface of the substrate member...
>
> A generally uniform coating of the receptive material or the blocking material is then applied to the substrate surface over the crosslinking agent layer. A mask is placed over the substrate, and the mask and substrate combination is irradiated with an energy source specifically selected to activate the photo-reactive group of the crosslinking agent. In its basic form, the "mask" serves to shield at least one area or section of the substrate member from the irradiating energy source and to expose at least one adjacent section to the energy source." (Emphasis added)

Like traditional masking techniques, the unmasked areas of the substrate are irradiated for selective binding of the first material. Irradiation activates the portion of the crosslinker that is exposed (or unshielded) by the mask. Referring to paragraph [0032],

> "As mentioned, the energy source is selected so that the reactive group of the exposed crosslinking agent is activated and thus attaches or crosslinks with the overlaying material (the receptive material or blocking material)." (Emphasis added).

After crosslinking the first material to the crosslinking layer, the mask is removed and the substrate is washed to remove unbound first material. Referring to paragraph [0033],

> "The receptive material or blocking material that was under the shielding areas of the mask (and thus not crosslinked with the crosslinking agent) is removed from the substrate in any suitable cleansing process, such as rinsing the substrate with water or buffer solution."

The second material is then added. The areas of the crosslinking layer that were previously shielded are then irradiated for binding to the second material. Referring to paragraph [0034],

> "A generally uniform layer of respective other material is then applied to the substrate member... The substrate member is then exposed to the energy source a second time so as to activate the remaining crosslinking agent in the areas of the substrate member that were shielded by the mask in the masking process." (Emphasis added)

Thus in Cohen et al. photo-masking remains the central method to selectively bind the receptive material and blocking material in designated areas. Accordingly, a combination with Cohen et al. still requires photo-masking.

Now, with respect to all claims, the blocking reagent itself includes a photoreactive group for covalent immobilization to a sensor, thus eliminating the need for a crosslinking layer and thus photo-masking. In other words, the blocking reagent in claims 79-80 can covalently attach to the substrate without such a photoreactive crosslinking layer and thus the substrate does not require masking. As such, the present invention provides not only a new blocking reagent but it permits a different technical approach to immobilization. That is, the traditional photo-masking technique as demonstrated by Cohen et al. is no longer necessary and thus a divergent technical approach is pursued.

Thus, viewing the technological approaches as a whole further demonstrates the present invention is not obvious over the technique employed by Cohen et al. Accordingly, Applicant respectfully requests the rejection be withdrawn.

C. Claim 81 is not obvious over Cohen et al. (US 2003/020728) in view of Pomato et al. (US 5,965,106) further in view of Clapper (US 5,744,515) and in light of Kamb et al. (US 2003/0027214) as applied to claim 80 and further in view of Caldwell et al. (US 5,516,703)

With respect to claim 81, the examiner argues that although the previous combination of references teach a pluronic surfactant blocking reagent they fail to teach the surfactant specifically being PLURONIC F-68. However the examiner cites Caldwell et al. as teaching modified pluronic surfactants, namely Pluronic F-68, immobilized to a substrate in order to provide a surface with minimum non-specific binding.

The deficiencies of Cohen et al. in view of Pomato et al. further in view of Clapper and in light of Kamb et al. are discussed above with respect to claims 79 and 80. Since neither claim 79 nor 80 is obvious over the cited references and the addition of Caldwell does not remedy the deficiency, claim 81, which depends from claim 79, is not obvious over the cited references and further in view of Caldwell et al.

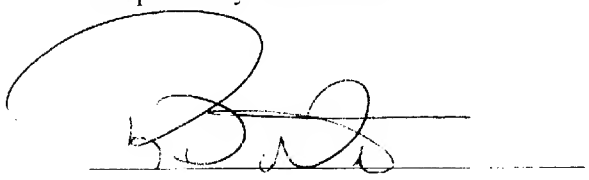
Accordingly, applicant respectfully requests the rejection be withdrawn and claim 81 allowed.

III.

Conclusion

In view of the arguments set forth above, applicant respectfully requests the rejections be withdrawn and all claims allowed.

Respectfully submitted,



February 2, 2010

Date

Raymond Wagenknecht

Reg. No. 50948

Biotech Beach Law Group PC
5677 Oberlin Dr., Ste 204
San Diego, CA 92121
USA
858-587-2510